REMARKS

Appreciation is expressed to Examiner Foster for the courteous and helpful interview of March 29, 2011. The foregoing amendments and following remarks reflect the substance of the interview.

Claim Language

The foregoing claim amendments address issues raised during the interview, the office action (pages 17 and 18) and in the advisory action of April 6, 2011. One of these involves the use of measured mid-proAM production in the body for determination of AM production in the body. (AM and ADM are used interchangeably herein to refer to adrenomedullin.) Without implying any agreement with the examiner's position that the claims must be limited in this regard, in order to expedite prosecution, corresponding language has been added. A second issue involves the preamble of the claim as discussed during the interview. Corresponding language has been added in the preamble and body indicating that the method is for the determination of production of AM. The third issue involves language related to quantitating AM.

The new language is clearly supported in the application, particularly in paragraphs 14 and 15. (Paragraph numbers refer to the published version of the application, US 2007/0212742.) See paragraph 14 regarding the object of providing a valid method "capable of giving reliable values for the physiological production of AM and/or its precursor in various pathological states . . ." As for the use of measured values of physiological production of mid-proAM as a measure of the values of physiological production of AM, instead of measured values of such AM production per se, this is also clearly supported. See, e.g., the abstract ("Method for the determination of adrenomedullin . . . in which the mid-regional partial peptide . . . is measured . . ."); paragraphs 14 and 15 ("It is therefore the Applicant's object to provide a valid method . . . capable of giving reliable values for the physiological production of AM . . . This object is achieved, according to the invention, if, instead of AM . . . a mid-regional partial peptide which contains the amino acids 42-95 of

pre-proAM (SEQ ID NO: 3) is determined . . ."); paragraph 18 ("To achieve the object of providing an assay method which reliably measures the formation of AM . . ."); and original claim 1 ("Method for the determination of adrenomedullin immunoreactivity in biological fluids for diagnostic purposes, characterized in that the mid-regional partial peptide . . . is measured."). The reference to "a healthy normal or pathological state" is included to be complete. As in any biological assay intended for diagnostics, not all patients will turn out to have a pathological condition or state; some will, of course, be in a healthy normal state. This is clear from use of the latter term (healthy normal) throughout the specification. See, e.g., paragraph 20 (line 2), paragraph 21 (line 2), paragraph 25 (line 1) and paragraph 28 (line 3), etc. See also Figures 1 and 2 referenced in these paragraphs.

In response to the examiner's advisory action, the previous reference to "levels" of the measures entities has been replaced with reference to "values." The latter term is employed in paragraph 14's description of the invention ("to provide a valid method . . . capable of giving reliable values for the physiological production of AM and/or its precursor in various physiological states . . ."). The relevant ordinary dictionary definition of "value" is: "the quantity or amount for which a symbol stands [to determine the *value* of x]." Webster's New World Dictionary, Second College Edition, page 1568 (1982) (attached). This term clearly provides the indication that "the mid-proAM level is being used as a proxy or surrogate in order to quantify the level of AM," as expressed by the examiner in the advisory action.

Should applicants have misunderstood any of the examiner's suggestions, she is urged to telephone the undersigned to expedite a resolution.

Unexpectedness

The remaining issue raised in the office action and discussed during the interview involved the fact that the stability of mid-proAM is unexpected. See the Struck Declaration.[1] It is the examiner's position that because of the nature of mid-proAM, a skilled worker would not have any particular expectation of its stability in

[1] The reference in the Struck Declaration at the end of its paragraph 3 to "Popio, et al.," should obviously be "Pio, et al."

comparison with the known instability of AM. In other words, the skilled worker would expect that the stability could be better, worse or the same. The showing of increased stability is merely one of these three "expected" possibilities. However, this rationale, it is respectfully submitted, is incorrect on at least two grounds.

The examiner's rationale does not reflect the law. The burden is on the PTO, not Applicants, to establish what would be the expectation of one of skill in the art. Here, there is only the bare allegation that, irrespective of the nature of the stability of mid-proAM, any result would be expected because it has to fall into one the three known possibilities; the same stability, higher stability or lower stability. This does not satisfy the burden on the PTO. There must be more than the mere fact that a result is "possible." Thus, the enhanced stability of mid-proAM cannot be said to be expected.

Moreover, even if the examiner's rationale were considered to be sufficient to establish that some degree of enhanced stability for mid-proAM over AM was expected, such an argument, based on the discussed alleged equivalent "possibilities," cannot realistically lead to an expectation for the very significant enhanced stability of mid-proAM. As established in the Struck Declaration with reference to Morganthaler et al., AM's notoriously poor stability includes the fact that in plasma its immunoreactivity decreases by 20 percent after storage for only 24 hours at room temperature. (Struck Declaration, page 2). In surprising contrast, Morganthaler, et al. establishes that mid-proAM is stable for at least 3 days in plasma at room temperature. See the passage bridging pages 2 and 3 of the Struck Declaration, with reference to Morganthaler, e.g., its Figure 3 and the first paragraph of its Discussion on page 1828. This surprisingly enhanced stability for mid-proAM includes stability for at least 14 days at 4 °C and for one year at -20°C.

Even if it were reasonable to expect from the fact that AM and mid-proAM are different peptides, that they would have different stabilities, nothing about these peptides of record leads a skilled worker to reasonably expect the vastly superior stability of mid-proAM. Under any reasonable scientific expectation, the significant

unexpected advantage described in the penultimate paragraph on page 3 of the Struck Declaration, is unexpected.

Further in this regard, AM and mid-proAM are peptide fragments derived from the same precursor, preproadrenomedullin. Although they are different fragments, they are still related in this sense. This is a factor indicating a relationship between the peptides. This could support the expectation that, like AM, mid-proAM could also be unstable. In any event, even if the examiner finds this fact to be irrelevant, it is certainly no less relevant than the fact on which the examiner relies, i.e., that the two peptides at issue are simply different in structure.

As for the double patenting rejections, as pointed out on the last page of the response of December 7, 2010, given that all claims are believed now to be allowable, under M.P.E.P. §804(I)(B)(1), all double patenting rejections (other than those based on 12/374,757) should be withdrawn since all of the cited applications were filed later than the above-identified application. As for 12/374,757, this is now USP 7,915,002. However, all of the claims are non-obvious over the claims of '002. Nothing in the latter claims suggests that values measured for production of mid-proAM can be used, instead of values of production of AM itself, to represent the recited production of AM. Thus, the double patenting rejection must be withdrawn.

In view of all the foregoing, it can be seen that all claims are allowable. Should the examiner have any further suggestions for an expedited allowance, she is courteously requested to telephone the undersigned.

Respectfully submitted,

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